(b) [Reserved]

[39 FR 11680, Mar. 29, 1974, as amended at 42 FR 36994, July 19, 1977; 52 FR 15892, Apr. 30, 1987; 52 FR 30055, Aug. 12, 1987; 55 FR 31779, Aug. 3, 1990; 57 FR 58374, Dec. 9, 1992; 58 FR 49898, Sept. 23, 1993; 59 FR 4218, Jan. 28, 1994]

EFFECTIVE DATE NOTE: At 60 FR 52507, Oct. 6, 1995, in § 310.201, paragraphs (a)(10) and (a)(15) were removed and reserved, effective October 7, 1996.

Subpart D—Records and Reports

§ 310.303 Continuation of long-term studies, records, and reports on certain drugs for which new drug applications have been approved.

(a) A new drug may not be approved for marketing unless it has been shown to be safe and effective for its intended use(s). After approval, the applicant is required to establish and maintain records and make reports related to clinical experience or other data or information necessary to make or facilitate a determination of whether there are or may be grounds under section 505(e) of the act for suspending or withdrawing approval of the application. Some drugs, because of the nature of the condition for which they are intended, must be used for long periods of time—even a lifetime. To acquire necessary data for determining the safety and effectiveness of long-term use of such drugs, extensive animal and clinical tests are required as a condition of approval. Nonetheless, the therapeutic or prophylactic usefulness of such drugs may make it inadvisable in the public interest to delay the availability of the drugs for widespread clinical use pending completion of such long-term studies. In such cases, the Food and Drug Administration may approve the new drug application on condition that the necessary long-term studies will be conducted and the results recorded and reported in an organized fashion. The procedures required by paragraph (b) of this section will be followed in order to list such a drug in § 310.304.

(b) A proposal to require additional or continued studies with a drug for which a new drug application has been approved may be made by the Commissioner on his own initiative or on the petition of any interested person, pursuant to part 10 of this chapter. Prior to issuance of such a proposal, the applicant will be provided an opportunity for a conference with representatives of the Food and Drug Administration. When appropriate, investigators or other individuals may be invited to participate in the conference. All requirements for special studies, records, and reports will be published in § 310.304.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 4714, Jan. 25, 1976; 42 FR 15674, Mar. 22, 1977]

§ 310.304 Drugs that are subjects of approved new drug applications and that require special studies, records, and reports.

Listed below are the new drugs and requirements referred to in § 310.303:

(a) [Reserved]

(b) *Methadone.* Methadone may be used as an analgesic in severe pain, for the detoxification of narcotic addicts, and as an oral substitute for heroin or other morphine-like drugs, in the maintenance treatment of narcotic addicts, pursuant to the conditions established in § 291.505. Further data and information are required to establish the safety and effectiveness of methadone under a variety of conditions during widespread and long-term use. In view of the tremendous public health and social problems associated with the use of heroin, the demonstrated usefulness of methadone in treatment, the lack of a safe and effective alternative drug or treatment modality, the need for additional safety and effectiveness data on methadone for narcotic addict treatment and the danger to health that could be created by uncontrolled distribution and use of methadone for narcotic addict treatment, the Commissioner of Food and Drugs finds that it is not in the public interest either to withhold the drug from the market until it has been proved safe and effective under all conditions of use for narcotic addict treatment or to grant full approval for unrestricted distribution, prescription, dispensing, or administration of methadone for this use. The Commissioner therefore concludes that it is essential to the public interest to prescribe detailed conditions for safe

and effective use of methadone for narcotic addict treatment, utilizing the IND and NDA control mechanisms and the authority granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, to assure that the required additional information for assessing the safety and effectiveness of methadone is obtained, to maintain close control over the safe distribution, administration, and dispensing of the drug, and to detail responsibilities for such control. The conditions established in §291.505 constitute a determination of the appropriate methods of professional practice in the medical treatment of the narcotic addiction of various classes of narcotic addicts with respect to the use of methadone, pursuant to section 4 of the Comprehensive Drug Abuse Prevention and Control Act of 1970.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 9546, Mar. 5, 1976; 41 FR 28263, July 9, 1976; 42 FR 46710, Sept. 16, 1977]

§310.305 Records and reports concerning adverse drug experiences on marketed prescription drugs for human use without approved new drug applications.

(a) *Scope.* FDA is requiring manufacturers, packers, and distributors of marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application to establish and maintain records and make reports to FDA of:

(1) All serious, unexpected adverse drug experiences associated with the use of their drug products;

(2) Any significant increase in the frequency of a serious, expected adverse drug experience; and

(3) Any significant increase in the frequency of therapeutic failure (lack of effect).

These reports will enable FDA to protect the public health by helping to monitor the safety of marketed drug products and to ensure that these drug products are not adulterated or misbranded.

(b) *Definitions.* The following definitions of terms apply to this section:

(1) *FDA* means the Food and Drug Administration.

(2) *Adverse drug experience* means any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

(3) *Unexpected* means an adverse drug experience that is not listed in the current labeling for the drug product and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

(4) *Serious* means an adverse drug experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

(5) *Increased frequency* means an increase in the rate of occurrence of a particular adverse drug experience, e.g., an increased number of reports of a particular adverse drug experience after appropriate adjustment for drug exposure.

(c) *Reporting requirements—15-day ''Alert reports.''* (1)(i) Any person whose name appears on the label of a marketed prescription drug product as its manufacturer, packer, or distributor shall report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible but in any case within 15 working days of initial receipt of the information. Each report shall be accompanied by a copy of the current labeling for the drug product.

(ii) A person identified in paragraph (c)(1)(i) of this section is not required to submit a 15-day ''Alert report'' for an adverse drug experience obtained from a postmarketing study (whether